

Remarks/Arguments

Claims 1-25 and 27-45 are pending in the present application. In view of the finality of the restriction requirement, claims 1-25 are under examination and claims 27-45 have been withdrawn from consideration.

Rejection under 35 U.S.C. § 103

Claims 1-25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Genentech (Basey *et al.*; WO 99/57134) in view of Grandics *et al.* (US 5,571,720).

According to the Examiner (see page 3 of the Office Action), “it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use a salt gradient in the ion exchange chromatography system of protein purification of Genentech, because Grandics *et al.* advantageously teaches the use of a salt gradient in a similar ion exchange chromatography system for cell culture protein purification, and the use of the salt gradient for purifying any protein as in Genentech would have merely been a matter of optimization by a protein research scientist versed in the methods of protein purification, as guided by the results sought.”

The Examiner adds, without further explanation, that “its is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.” (Office Action, page 3)

Applicants disagree and respectfully traversed the rejection.

The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. See MPEP, 2141.

As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are as follows:

- (A) Determining the scope and contents of the prior art;
- (B) Ascertaining the differences between the prior art and the claims in issue;
- (C) Resolving the level of ordinary skill in the pertinent art; and
- (D) Determining the issue of obviousness or non-obviousness.

(A) Determining the scope and contents of the prior art

Basey *et al.* teaches protein purification by ion exchange chromatography, but does not teach an ion exchange chromatography system where a salt gradient is employed.

Grandics *et al.* teach the use of an integrated cell culture protein purification system using an ion exchange chromatography using a single linear salt gradient.

(B) Ascertaining the differences between the prior art and the claims in issue

Claim 1 of the present application, as amended, is directed to:

“A method for purifying a polypeptide from a composition comprising the polypeptide and contaminants, which method comprises the sequential steps of:

- (a) loading the composition onto an ion exchange resin with an equilibration buffer having a first salt concentration;
- (b) washing the ion exchange resin with a wash buffer until a predetermined protein concentration is measured in the flowthrough, wherein the salt concentration of the wash buffer increases from an initial, second salt concentration that is greater than the salt concentration of the equilibration buffer, to a final, third salt concentration;
- (c) passing a fixed volume of wash buffer at the final, third salt concentration over the ion exchange resin; and
- (d) eluting the polypeptide from the ion exchange resin with elution buffer that has a salt concentration that is greater than the final salt concentration of the wash buffer.” (Emphasis added)

Claim 1 of the present application teaches protein purification via cation exchange chromatography employing different salt gradients resulting in a non-linear salt gradient. Thus the subject matter recited in claim 1 is distinctly different than the combined disclosures of the cited reference, which, at best, could suggest the use of a single, linear salt gradient.

(C) Resolving the level of ordinary skill in the pertinent art

The level of the skill in the art of protein purification is relatively high and is represented by a scientist having an advanced degree and several years of laboratory or industry experience.

(D) The cited combination of references does not make obvious the invention claimed

The disclosure of Grandics *et al.* shows that using a linear salt gradient is within the level of ordinary skill in the art of chromatography as applied to protein purification. However, the purification steps of the current application, as recited in claim 1, include the application of more than only one salt gradient which results in a non-linear salt gradient. A non-linear salt gradient is not disclosed or suggested by the combined disclosures of Genentech and Grandich *et al.* According to the Examiner, “it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.” However, Applicant respectfully points out that use on a non-linear salt gradient would not, without hindsight, have been reasonably expected to succeed, as evidenced by the use of a single linear salt gradient in Grandics *et al.*

The challenge of obtaining high yield and high purity in protein purification in ionic exchange chromatography was solved in the present application by applying a non-linear gradient of ionic strength. It was found that the product species was able to be obtained at highest yield and purity levels upon imposing a series of increasingly shallow rates of increase in ionic strength at increasing elution times. This finding, which is far from obvious, is not suggested by Genentech or Grandics *et al.*, when taken alone or in combination. Thus, it could not have been obvious that applying a non-linear gradient would effect the desired high levels of protein yield and purity.

Conclusion

As Basey *et al.* (Genentech) does not employ a salt gradient and as Grandics *et al.* discloses the use of only a single linear salt gradient in protein purification, combination of the two references would not lead to the invention or to the superior results obtained using a non-linear gradient of increasing ionic strength. As the results obtained in the present application using non-linear gradient are unexpectedly superior over the results achieved or suggested by the combination of Basey *et al.* and Grandics *et al.*, the cited combination does not render obvious, the invention claimed in the present application.


Accordingly, applicant's respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103 over Basey *et al.* in view of Grandics *et al.*

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (**Attorney Docket No.: 39766-0113A**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully Submitted,

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